Case Report

Ertapenem-associated neurotoxicity in the spinal cord injury (SCI) population: A case series

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Context: Ertapenem, a broad spectrum carbapenem antibiotic, is used often in Spinal Cord Injury (SCI) patients due to increased risk factors for multi-drug resistant (MDR) infections in this population. Neurotoxicity, specifically seizures, due to ertapenem is a known adverse effect and has been described previously. Other manifestations such as delirium and visual hallucinations have rarely been reported, and no literature, to the best of our knowledge, specifically describes these effects solely in the SCI population.

Findings: Four cases of mental status changes and hallucinations in SCI patients attributed to ertapenem therapy are described. Onset of symptoms began between one and six days following initiation of ertapenem and resolved between two to 42 days following discontinuation. Based on the Naranjo probability scale, a probable relationship exists between the adverse events and ertapenem for three out of the four cases. Possible overestimation of renal function and hypoalbuminemia may be contributing factors to the noted adverse reactions.

Conclusion/Clinical Relevance: The cases described highlight the importance of recognizing ertapenem-associated hallucinations in SCI patients. The population is particularly vulnerable due to risk factors for MDR infections necessitating ertapenem use, possible overestimation of renal function, and a high prevalence of hypoalbuminemia.

Keywords: Ertapenem, Hallucination, Spinal cord injury

Introduction

Ertapenem is a broad spectrum carbapenem antibiotic with activity against Gram-positive and Gram-negative organisms. Pharmacokinetic properties unique to ertapenem include high protein binding caused by increased lipophilicity and a net negative charge, which provides a long half-life and allows for once daily dosing.[1] Indications for use include a variety of infections such as complicated urinary tract, intra-abdominal, and skin and skin structure infections.[2] Its stability against hydrolysis by extended spectrum beta-lactamases (ESBL) allows it to be at the forefront of treatment for many multi-drug resistant (MDR) organisms, particularly in the *Enterobacteriaceae* group.[1,2] Though all hospitalized patients can be susceptible to MDR infections, the Spinal Cord Injury (SCI) patient population, in particular, are at risk due to underlying disease pathology leading to an increased prevalence of invasive interventions such as urinary catheterization and mechanical ventilation, as well as frequent utilization of the healthcare system.[3,4] Although neurotoxicity including seizures due to ertapenem is a known adverse effect and has been described previously,[5] other manifestations such as delirium and visual hallucinations have rarely been reported;[6–14] and no literature, to the best of our knowledge, exists specifically describing these effects solely in the SCI population. We describe 4 cases of mental status changes and hallucinations in SCI patients attributed to ertapenem therapy.

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Case reports

Case 1

A 47 year-old male (height 165 cm, weight 68 kg) with a history of quadriplegia (American Spinal Injury Association (ASIA) category A spinal cord injury (C4-5)), neurofibromatosis, neurogenic bowel and bladder, recurrent urinary tract infections (UTI), and respiratory failure with subsequent tracheostomy and use of nighttime ventilator was admitted for care of bilateral

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ischial wounds with future plans for flap surgery. While admitted, the patient developed a suspected UTI and ceftazidime was started empirically. Urine cultures returned with >100,000 *Citrobacter koseri,* resistant to ceftazidime, so antibiotic therapy was switched to ertapenem 1000 mg IV daily. The patient's serum creatinine (SCr) at that time was 0.4 mg/mL, which was at his baseline.

On day five of ertapenem therapy, the patient was noted to be confused, asking the same questions repetitively. On day six, he was documented as being oriented to person only and remained in a confused and forgetful state for the next three days. Medications at the time of confusion included dantrolene, diazepam, baclofen, tizanidine, cholecalciferol, simethicone, potassium, docusate enemas, and various topicals for wound care. Psychiatry was consulted and determined that confusion was likely related to delirium and that medications were probably not the etiology. All labs checked around this time returned unremarkable. A CT of the head was performed seven days into ertapenem therapy and revealed only mild cerebral atrophy. Haloperidol was given as needed for agitation, baclofen dosing was tapered down and eventually stopped, and diazepam dosing was tapered down. Ertapenem was discontinued on the ninth day of therapy and flap surgery was rescheduled due to the patient's delirium. His mental status continued to improve over the next few days following ertapenem discontinuation, however never fully returned to baseline until documented as such six weeks later. Flap surgery was performed a month after discontinuation of the ertapenem. Further use of ertapenem was avoided during this admission but various beta lactam antimicrobials, including imipenem/cilastatin, were used after this incident and confusion never returned.

Case 2

A 59 year-old male (178 cm, 91 kg) with a history of incomplete C5-7 quadriplegia (ASIA B) status post boiler room explosion (1973), post-traumatic C4-T1 syringomyelia, hypothyroidism, chronic obstructive pulmonary disorder, hypertension, hyperlipidemia, depression, diabetes mellitus, peripheral neuropathy, obstructive sleep apnea, iron deficient anemia, vitamin D deficiency, chronic hyponatremia, neurogenic bladder, and essential tremor was admitted for gastrostomy (G) tube assessment and replacement after experiencing problems with leakage. A couple of days after admission, the patient had a new fever (39.1°C) along with leukocytosis (13×10^9/L) and a urinalysis suggestive of infection. Based on previous urine cultures, IV vancomycin and ertapenem 1000 mg IV daily were started empirically. Patient's SCr at that time was 0.3 mg/dL which was at his baseline.

On day 10 of ertapenem therapy, the patient complained to the nurse that he was having visual hallucinations; specifically that he was seeing a girl that he knew was not there. Ertapenem therapy was discontinued the day after as the course of therapy was complete. Despite infection resolution (no further fevers, WBC had returned to normal), the patient continued to have visual hallucinations, described as seeing dogs and cats and talking to the Pope. Additionally, he was experiencing tremors and confusion. Pertinent medications at this time included metronidazole, methadone, oxycodone, diazepam, baclofen, pregabalin, simvastatin, levothyroxine, atenolol, lansoprazole, risperidone, oxybutynin chloride, bupropion, and primidone. Neurology was consulted and determined that hallucinations were possibly a side effect of ertapenem. Psychiatry service also evaluated the patient and recommended to restart the bupropion at three times a day dosing (since recently titrated down), continue to hold zolpidem, titrate down diazepam at a slower rate, and to continue risperidone for psychosis and confusion. Other possibilities on the differential diagnosis included a recent vascular event or a simple partial occipital seizure. Basic laboratory evaluations monitored around this time remained unremarkable. A head CT scan was completed, but was limited and showed no acute intracranial changes. An EEG the same day demonstrated a mild to moderate degree of diffuse slow wave abnormality, indicating the presence of generalized neurophysiological disturbance. Six days after stopping the ertapenem, the patient's mentation returned to baseline and he was discharged four days later.

Case 3

A 90 year-old male (170 cm, 58 kg) with a history of L1 paraplegia (ASIA C), hypertension, glaucoma, alcohol abuse in remission, decubitus ulcers, and peripheral vascular disease was admitted for ischial wound management. The patient initially received conservative wound management but eventually required a fasciocutaneous flap closure of the right ischial pressure sore. The bone culture that was obtained during the flap surgery did not grow any organisms and the wound tissue culture from the same day grew out *S. epidermidis.* As there was bone visible with the wound and the pathology was consistent with osteomyelitis, the patient was treated for osteomyelitis to avoid a potential flap failure if left untreated. Ertapenem 1000 mg IV daily was started in light of recent urine culture growing ESBL *P. mirabilis* and also for general coverage of other

Gram-negative organisms and anaerobes for an intended duration of 6 weeks with further follow up. The patient's SCr at that time was 1.16 mg/dL, which was at his baseline.

Nine days after starting ertapenem, the patient was noted to have intermittent periods of confusion and visual hallucinations. He was not oriented to date, was giving illogical answers to questions, and was found by the nursing staff talking aloud in his room for an extended period of time, as if talking to someone. Psychiatry was consulted and confirmed the patient's confused state, thought to be likely due to some type of delirium. Ertapenem was switched to meropenem the day after the development of altered mental status, per recommendation of Infectious Diseases. Other pertinent medications at this time included docusate/sennosides, furosemide, hydralazine, lisinopril, metoprolol, oxybutynin chloride, simvastatin and terazosin. Risperidone was started per recommendation of Psychiatry. Apart from elevated ESR and CRP levels, pertinent labs around this time were not remarkable. The confusion and hallucinations continued but were improving, and by the sixth day after discontinuation of the ertapenem, the patient was noted to be back at baseline mental status. The patient's risperidone dose was titrated down and he successfully completed treatment for the osteomyelitis with meropenem with no further documentation of mental status changes.

Case 4

A 72 year-old male (180 cm, 103 kg) with a history of T4 paraplegia (ASIA C), diabetes mellitus, cellulitis, cocaine dependence, chronic obstructive pulmonary disorder, obstructive sleep apnea, multiple flap surgeries for pressure ulcers, elevated PSA and history of bladder stones was admitted for treatment of a left ischial ulcer. CT imaging revealed osteomyelitis and the patient was initially treated with wound care. Though recommended, a bone biopsy was not performed and the patient was treated with oral antibiotics. A month later they were discontinued due to pathology demonstrating chronic osteomyelitis. The patient eventually underwent debridement of the ischial ulcer, osteotomy and bi-planar flap reconstruction surgery six weeks later. Preliminary bone culture results showed Gram-positive cocci, so empiric IV vancomycin was started. Final culture results grew *Enterobacter cloacae* and *Staphylococcus epidermidis.* Ertapenem 1000 mg IV daily was started two days after the vancomycin was initiated. The patient's SCr at the time of ertapenem initiation was elevated from his baseline of $<$1.0 mg/dL to 1.26 mg/dL.

About 36 hours after starting vancomycin, the patient started experiencing twitching and weakness in his right arm. Neurology was consulted and determined that possible etiologies of the patient's myoclonus could be either infection-related due to osteomyelitis or possibly uremia related to vancomycin toxicity, as the vancomycin trough level had been supratherapeutic at 23.2 mcg/mL when last checked. No new medications had been initiated other than the antibiotics. Pertinent medications at the time included loperamide, tizanidine, atorvastatin, terazosin, diltiazem, allopurinol, isosorbide mononitrate, metoprolol, pregabalin, baclofen, omeprazole, losartan, amlodipine, and tramadol. ESR and CRP levels were elevated, but other basic labs remained unremarkable. An EEG was performed that showed a mild to moderate severity of diffuse slow wave abnormality suggesting a presence of a generalized neurophysiologic disturbance compatible with a mild to moderate

Table 1 Characteristics and clinical features of 4 SCI patients with ertapenem-induced neurotoxicity.

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Male
Age (year)	47	59	90	72
Ertapenem dose (mg/day)	1000	1000	1000	1000
Duration of Ertapenem (days)	8	10	10	1
Onset (days)[a]	5	6	6	1
Resolution (days)[b]	42	10	9	2
$CrCl_{CG}$ (mL/min)[c,d]	$>$100	$>$100	35	65
$CrCl_{SCI}$ (mL/min)[c,d]	49	50	30	39
Albumin (3.5–5.5 g/dL)[c]	3.1	2.4	2.3	2.6
Naranjo Probability Scale [15]	probable (6)	probable (6)	probable (6)	possible (4)

[a]Days of ertapenem until onset of hallucinations/delirium.
[b]Days from discontinuation of ertapenem until resolution of hallucinations/delirium.
[c]At time of ertapenem initiation.
[d]CG, Cockcraft-Gault; SCI, "spinal cord injury" equation; if patient was obese, adjusted body weight was used in the Cockcraft-Gault calculation.

encephalopathy. A day after starting ertapenem, the patient was witnessed having episodes of new hallucinations. Infectious Diseases service was re-consulted and recommended to hold antibiotics as per discussion with Plastics service the patient's wounds looked clean intra-operatively and the significance of the bone culture results (which were broth isolates) were being questioned. In addition, the patient did not have any fevers or leukocytosis to suggest active infection. Thus, both the vancomycin and ertapenem were discontinued the day after starting the ertapenem. Both the myoclonus and hallucinations appeared to have been resolved two days later.

Characteristics and clinical features of the four cases described are depicted in Table 1.

Discussion

Similar to other carbapenems, it is known that ertapenem can cause neurological complications, such as seizures;[5] however, the association of ertapenem with hallucinations and delirium is less well described. A search of PubMed (January 2000 – September 2016) for literature on ertapenem-related neurotoxicity and hallucinations as well as a review of the references of the source articles discovered descriptions of these symptoms in 16 patients in nine case reports.[6–14] Among the previously published literature, only one case reported altered mental status associated with ertapenem use in an SCI patient. Duquaine *et al.* described neurotoxicity in a 79 year-male with ASIA B SCI who received ertapenem for osteomyelitis.[6] After one week of therapy, he developed confusion with nonsensical speech. Ertapenem was discontinued and his mental status returned to baseline within one week. Upon re-challenge, he again experienced altered mental status, which resolved one week after discontinuing ertapenem.

Collectively, other studies reported an onset of symptoms ranging from two to 14 days after ertapenem initiation with resolution within two to 14 days after discontinuation (Table 2). The clinical courses of our patients were similar to those previously described with the exception of Case 1, whose mental status was not documented as at baseline until six weeks after receiving ertapenem. Oversight in documentation or additional causes for confusion may account for the prolonged duration of symptoms that were reported. Use of the Naranjo probability scale[15] indicated a probable relationship between the adverse events and ertapenem for Cases 1, 2, and 3 (all scored 6 with range of 5–8 indicating probable relationship) (Table 1). A possible relationship (score of 4 with range of 1–4 indicating possible relationship) was found with Case 4 given the development of myoclonus while on IV vancomycin alone, hallucinations once on vancomycin and ertapenem, and resolution of symptoms when both antibiotics were stopped. Although its role in this case could not be completely ruled out, there are no reported adverse events involving vancomycin and hallucinations in the package insert or published literature.[16]

Despite the association between ertapenem and delirium and/or hallucinations in these cases as well as previous reports, the mechanism is unclear. Carbapenems are known to cause seizures through inhibition of $GABA_A$ but whether these effects could cause non-seizure neurotoxicity is unknown.[5,6] Certain pharmacokinetic properties of ertapenem including high level of protein binding, long half-life, lipophilicity, central nervous system penetration along with primary elimination by the kidneys may all contribute to the development of these adverse drug reactions, specifically in the SCI population. Although the association of neurotoxicity and seizures with excessive dosing of ertapenem is known,[3] the majority of ertapenem-related neurotoxicity cases (excluding convulsions) described in the literature appeared to have occurred when the drug was dosed appropriately based on CrCl. Previous studies have noted the need for caution when using ertapenem in elderly patients since lower muscle mass can result in decreased creatinine levels, potentially causing the Cockcroft-Gault equation to overestimate renal function and lead to inappropriate dosing.[14] Similarly, SCI patients often have decreased creatinine production due to muscle atrophy as a result of muscle denervation, again causing a falsely elevated depiction of renal function.[17] Because of this, alternate methods for more accurately determining renal function in SCI have been proposed and validated.[18,19] Table 1 lists the differences in CrCl of the four Case patients using the standard Cockcraft-Gault equation ($CrCl_{CG}$) as well as the "spinal cord injury equation" ($CrCl_{SCI}$) as described by Lee and colleagues.[18] Careful attention to methods for determining renal function and thus dosing of ertapenem may help to avoid potential adverse events related to treatment.

Of note, all four case patients presented here had chronic hypoalbuminemia (HA) (Table 1). HA has been described in the SCI population, specifically in the setting of sepsis and infection.[19] In one study, infusion of tracer albumin demonstrated a leak from the vascular system in subjects with SCI, in the setting of paraplegia and tetraplegia.[20] As low albumin levels can cause higher levels of free drug, especially in a highly protein-bound drug such as ertapenem, it is unclear whether this, in conjunction with the other

Table 2 Summary of ertapenem-Induced delirium and hallucinations in previous case reports.

Study	Patient demographics (age, sex)	Ertapenem dose (mg)	Renal function (ml/min)	Dose appropriate (Y/N)	Symptoms	Onset (Days)[a]	Resolution (Days)[b]	Symptom return on rechallenge (Y/N/NA)
Duquaine	79 y/o M	1000	>30	Y	Altered mental status, miosis	7	7	Y
Duquaine	70 y/o M	1000	<30	N	Visual hallucinations, obtundation, metabolic acidosis requiring intubation	5	2	NA
Wen	78 y/o F	500	<10	Y	Agitation, cognitive impairment, myoclonus	4	14	NA
Wen	70 y/o F	500	<10	Y	Hallucinations, cognitive impairment, myoclonus, asterixis	5	14	NA
Oo	54 y/o M	1000	>30	Y	Confusion, disorientation visual hallucination, myoclonus	5	10	NA
Oo	48 y/o M	1000	NR	---	Confusion, disorientation, visual and auditory hallucinations, agitation	10	3	NA
Peinado	76 y/o F	1000	<30	N	Visual hallucinations, gait instability, focal seizure	2	NR	Dose decreased to 500 with symptom resolution
Peinado	44 y/o M	1000	NR	---	Photopsia	NR	NR	Dose decreased to 500 with symptom resolution
Lee	72 y/o M	500	HD	Y	Agitation, disorientation, visual hallucination	5	7	NA
Lee	66 y/o M	500	HD	Y	Disorientation, Seizure	4	7	NA
Lee	79 y/o F	500	HD	Y	Agitation, confusion, visual hallucination	3	7	NA
Lee	73 y/o M	500	HD	Y	Confusion, visual hallucination	4	8	NA
Apocada	42 y/o F	NR	NR	---	Visual hallucinations, altered mental status, myoclonus	7	2	NA
Shea	84 y/o F	1000	>30	Y	Confusion, visual hallucinations	7	14	NA
Kong	58 y/o M	NR	NR	---	Visual hallucinations	NR	NR	Y
Veillette	71 y/o M	1000	>30	Y	Disorientation, visual hallucinations, suicidal ideations	14	3	NA

Y, yes; N, no; NA, not applicable; NR, not reported; HD, hemodialysis.
[a]Days of ertapenem until onset of symptoms.
[b]Days from discontinuation of ertapenem until resolution of symptoms.

factors listed above, contributed to excessive ertapenem drug levels leading to neurotoxic effects.

Conclusions

This report highlights the importance of recognizing ertapenem-associated hallucinations in SCI patients. The population is particularly vulnerable due to risk factors for MDR infections necessitating ertapenem use, possible overestimation of renal function, and a high prevalence of HA.

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